INHIBITORS OF MEMAPSIN 2 AND USE THEREOF

Abstract

Methods for the production of purified, catalytically active, recombinant memapsin 2 have been developed. The substrate and subsite specificity of the catalytically active enzyme have been determined. The substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate that can inhibit the function of memapsin 2. The substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2. The substrate analogs contain at least one analog of an amide bond which is not capable of being cleaved by memapsin 2. Processes for the synthesis of two substrate analogues including isosteres at the sites of the critical amino acid residues were developed and the substrate analogues, OMR99-1 and OM99-2, were synthesized. OM99-2 is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-state isostere hydroxyethylene group (Figure 1). The inhibition constant of OM99-2 is1.6 x 10^{-9} M against recombinant pro-memapsin 2. Crystallography of memapsin 2 bound to this inhibitor was used to determine the three dimensional structure of the protein, as well as the importance of the various residues in binding. This information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors to memapsin 2, useful in diagnostics and for the treatment and/or prevention of Alzheimer's disease.